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REVIEW

Hypophosphatasia: diagnosis and clinical signs – a dental surgeon perspective

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Summary

Background. Hypophosphatasia (HPP) is a rare inherited metabolic disease in which mutations in the *ALPL* gene (encoding tissue-nonspecific alkaline phosphatase) result in varying degrees of enzyme deficiency. HPP manifests in a spectrum of symptoms, including early primary tooth loss (root intact) and alveolar bone mineralisation defects.

Objective. To provide an overview of HPP for dental professionals to help recognise and differentially diagnose patients for appropriate referral to a specialist team.

Methods. A non-systematic review of publications on HPP was performed.

Results. Different forms of HPP are described, along with characteristic symptoms and laboratory findings. Diagnosis is challenging due to the rareness and variable presentation of symptoms. Low alkaline phosphatase levels are a signature of HPP, but reference ranges vary according to gender and age. Key features are defined and management strategies discussed, focusing on enzyme replacement therapy. Finally, a patient registry aimed at better defining the prevalence of HPP and raising awareness is described.

Conclusions. HPP is a rare disease with a wide spectrum of manifestations, with orodental symptoms featuring prominently in the natural history. Dental professionals may be positioned at the beginning of the diagnostic pathway; thus, recognition of HPP features for timely referral and optimal disease management is important.

Introduction

Hypophosphatasia (HPP; On Line Mendelian Inheritance in Man [OMIM®] #146300, 241500, 241510) is a rare genetic disorder with autosomal dominant and autosomal recessive inheritance. It is characterised by a mineralisation deficit affecting the bones and teeth, which is associated with deficient and reduced enzymatic activity of tissue-nonspecific alkaline phosphatase (TNSALP)[1–4]. Mutations of the *ALPL* gene (1p36.1-p34), which encodes TNSALP, are responsible for the reduction in enzymatic activity. TNSALP is expressed in the liver, bones, and kidneys, and also found in the enamel, dentine, cementum, and alveolar bone[5].

In the event of reduced enzymatic activity of TNSALP, substrates that are not broken down (pyridoxal 5′-phosphate, inorganic pyrophosphate, and phosphoethanolamine) build up and produce toxic effects; for example, inorganic pyrophosphate is a powerful mineralisation inhibitor[6]. These substrates may be detected in blood and urine[7–13]. Six clinical forms of HPP that relate to the age at onset of the symptoms have been described:

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A book published in 2012 entitled 'Hypophosphatasie, de l'ornière au gué' tells the story of a fight for disease diagnosis and treatment and provides insight into the daily life of patients with HPP and their families through the eyes of twenty expert witnesses (patients, families, charities, doctors, scientists, manufacturers). It can be ordered via the association's website: http://livre.hypophosphatasie.com. Prof. Agnès Bloch-Zupan has chaired the scientific board of the association since 2008.

perinatal (fatal), benign prenatal, infantile, childhood, adult, and odonto-HPP, which is limited to orodental manifestations (Table 1)[4,11–14]. Disease severity is highly variable, but typically inversely proportional to the age at onset of the initial symptoms[11,14]; however, in reality, the clinical presentation of the disease is more complex than this classification suggests.

The perinatal form is the most severe and results, *in utero* or at birth, in the almost total absence of bone mineralisation[11]; for example, reports are not uncommon of an almost complete lack of mineralisation in the skull or rib cage. The benign prenatal form can be detected through bone-related symptoms in the prenatal period[12]. Its course is more favourable than the severe perinatal form[12].

The infantile form typically develops at around 6 months of age and results in severe bone deformities and rickets[13]. It may also present with respiratory complications, premature craniosynostosis, hypercalcaemia, and nephrocalcinosis[11]. Additionally, the onset of epileptic seizures secondary to the build-up of pyridoxal phosphate often occurs and is a sign generally incompatible with survival[13].

The childhood form of HPP appears >6 months and presents in very diverse forms. Bone deformities may be minor, and the disease may result only in the early loss of the primary teeth[13]; however, in some cases, it is associated with moderate HPP-related rickets, short stature, delayed walking or gait disorders, and pain in the lower limbs[11,15].

Adult HPP tends to manifest in middle age, but there is usually history of premature loss of primary teeth[13]. It involves early loss of the permanent teeth, which is usually associ-

Table 1. Key features of the six clinical forms of hypophosphatasia[4,11–14].

Form of HPP	Perinatal	Benign prenatal	Infantile	Childhood	Adult	Odonto-HPP
Age at onset of first signs/ symptoms	*In utero* and at birth	*In utero*	<6 months of age	≥6 months–18 years of age	≥18 years of age	Any age
Clinical signs and symptoms	Stillbirth Hypomineralisation Chest deformity Long-bone deformity Osteochondral spurs Radiolucencies into metaphyses Poorly ossified epiphyses Fractures Seizures Apnoea	Skeletal disease (poor skeletal mineralisation) *in utero* Foetal crowding Long-bone narrowing Benign postnatal course	Rickets Fractures Respiratory insufficiency/ failure Poor feeding/ weight gain Failure-to-thrive Hypotonia B_6-responsive seizures Craniosynostosis Nephrocalcinosis Hypercalcemia/ hypercalciuria	Rickets Skeletal deformity Poor healing or recurrent fractures Hypomineralisation Short stature Muscle weakness Missed motor milestones Chronic muscle/ joint/bone pain waddling Nephrocalcinosis	Fractures/ pseudofractures Osteomalacia Chondrocalcinosis Osteoarthropathy Pseudogout Chronic muscle/ joint/bone pain	No abnormalities of skeletal system Loss of alveolar bone
Dental features	N/A	N/A	Premature primary tooth loss	Premature tooth loss (incisors often first)	History of premature primary tooth loss Adult tooth loss Abnormal dentition	Early dental exfoliation (incisors) Reduced thickness of the dentin Enlarged pulp chambers of teeth Dental caries
Inheritance	AR	AD	AR	AR (frequent) or AD (rare)	AR or AD	AR or AD

AD, autosomal dominant; AR, autosomal recessive; N/A, not applicable.

ated with multiple fractures, osteomalacia, chondrocalcinosis, osteoarthropathy, and stress fractures. Some cases are associated with a family or personal history of moderate rickets during childhood[15].

Odonto-HPP is limited to dental manifestations alone and can occur at any age[13]. Alveolar bone loss is apparent, but otherwise no skeletal abnormalities are evident[11].

HPP is a chronic, disabling disease with multiple facets that must be taken into account. It presents as a continuum, from childhood to adulthood, and its clinical expression changes over the course of the patient's lifetime, in particular during certain periods (adolescence, menopause) or in response to specific events (fractures, ingestion of vitamin D)[13]. With increasing age, the problems of osteoarthritis, osteoporosis, nephrocalcinosis, muscle weakness, and repeated fractures may exacerbate the clinical situation[16].

The aim of this article was to provide an overview of HPP with the hope of raising disease awareness and aiding its recognition and correct management for the practicing dentist and dental surgeon.

Epidemiology

Based on molecular tests, the prevalence of severe HPP in Europe is estimated to be approximately 1 case per 300,000 individuals[17]. The incidence of moderate forms is without doubt higher than severe forms, possibly as high as 1 in 6370[17]; however, at present, there are between 80 and 100 known cases of HPP in France, including 70 patients with very severe forms (perinatal or infantile HPP), which suggests that these forms are largely underdiagnosed[17]. In Japan, the prevalence of severe perinatal lethal HPP, classified according to clinical features, is estimated to be approximately 2–3 cases per 100,000 births[18] and the incidence of the most severe forms of HPP in Canada was estimated to be approximately 1 in 100,000, but this figure is from a study published more than 50 years ago[19,20].

Clinical signs and characteristic symptoms

The key bone and dental manifestations of HPP are outlined in Table 1.

Bone symptoms

Bone fragility and deformities may be present *in utero* or at birth. Growth in stature and weight gain are poor in forms of HPP that manifest at an early age[15]. In childhood forms of HPP, the patient often finds it difficult or even impossible to walk (resulting in a limp and the use of crutches or a wheelchair). Pain, being late to sit up or walk, growth retardation, and muscle weakness are all warning signs for HPP. Associated symptoms are premature craniosynostosis with intracranial hypertension, plagiocephaly, or quite the opposite, the presence of a wide fontanelle that is slow to close, metaphyseal abnormalities, diaphyseal incurvation, and highly fragile bones[11,15].

Dental symptoms

Early loss of primary teeth, before age 3, may affect all teeth or just those in the incisor–canine region. The primary teeth are shed with their roots intact. The first sign is often tooth mobility, which leads the patient and their family to seek advice; subsequent radiographs reveal severe alveolar bone loss[15]. Early loss of primary teeth exists in all forms of HPP and should be part of the medical/dental history questionnaire for patients of all ages.

The clinical picture in older children and adults with HPP generally includes the early loss of all or some of the permanent teeth. There may be, however, no associated skeletal deformities, such as in odonto-HPP[15]. Such early tooth loss is not generally associated with an inflammatory and infectious context, which, if present, are warning signs of other general diseases[21,22]. Representative images from the childhood and adult forms of HPP are provided in Fig. 1[23].

Orodental repercussions of HPP are reported in all forms of the disease, including premature loss of primary teeth in infant and childhood forms; and early loss of permanent

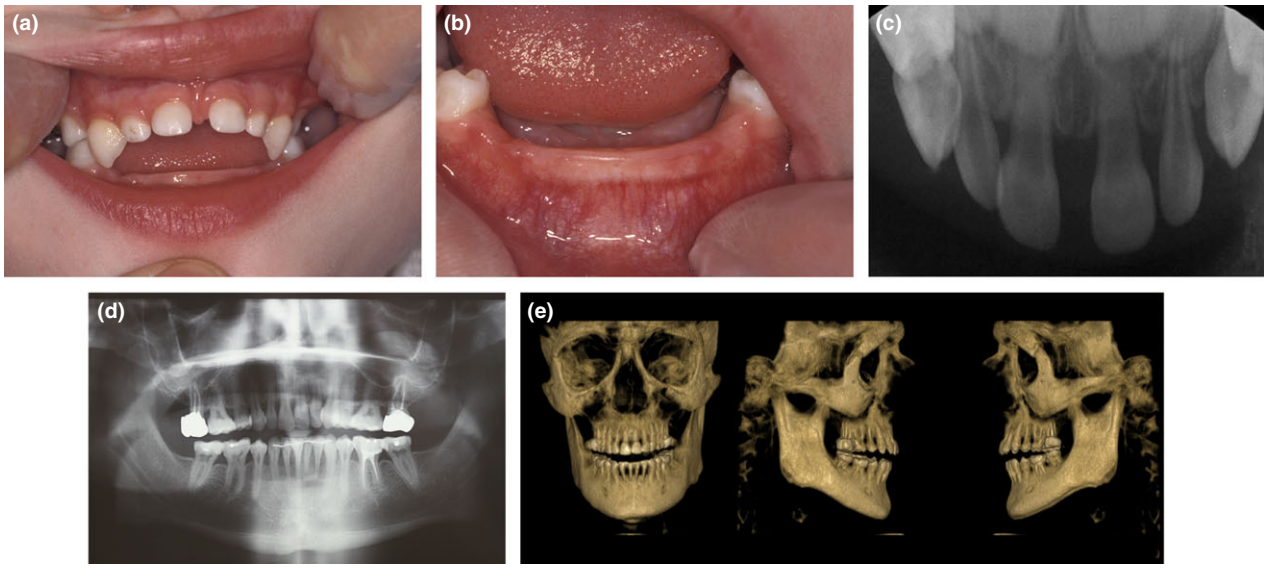

Fig. 1. (a–c) Early loss of primary teeth (83, 82, 81, 71, 72, 73) in a 30-month-old patient with a juvenile form of hypophosphatasia with 2 heterozygous A159T mutations (c.526G>A; c.648 + 1G>A). 71 and 81 were lost at 9 months. Upper incisors 52, 51, 61, 62 are moving. The alveolar bone has been resorbed. (d–e) Periodontal disease particularly in the anterior region in a 27-year-old adult with a moderate infant form of HPP due to mutations of the *ALPL* gene in the compound heterozygous form R119H/(G145V+Y246H). The patient's history includes the early loss of 12 primary teeth (53, 52, 51, 61, 62, 63, 73, 72, 71, 81, 82, 83) before 3 years of age. Figure originally published in *Alpha Omega News* 2014;166:23–26[23].

teeth, and sometimes periodontal disease, in adult HPP and in odonto-HPP[24]. The dysregulation of pyrophosphate causes abnormalities affecting the formation of the cementum covering the tooth root, which is essential for tooth structure and attachment to the alveolar bone[25], thereby contributing to early tooth exfoliation. Problems with the formation of dentine and amelogenesis also occur[26]. In children with HPP, hypercalcaemia may result in a poor appetite and eating problems, and severe dental caries[4]. Therefore, the dental surgeon is frequently one of the first healthcare professionals in a position to recognise the diagnosis of HPP, in particular in older children and adults with early unexplained orodental issues.

Differential diagnosis

Dental considerations

Early tooth loss can also occur in immune deficiencies associated with cyclic neutropenia (a disruption in granulopoiesis resulting in oscillations of available blood cells)[27], Papillon-Lefèvre syndrome (characterised by diffuse palmoplantar keratoderma and aggressive periodontitis)[28], Haim-Munk syndrome (characterised by hyperkeratosis and erythema)[29], Chediak-Higashi syndrome (characterised by recurrent infections and periodontal disease)[30] or as part of Ehlers-Danlos syndrome (VIII, IV; characterised by skin hyperextensibility, delayed wound healing, and other signs)[31], or even aggressive periodontal disease[32]. Dentinogenesis imperfecta occurs in about 50% of patients with osteogenesis imperfecta and is characterised by transparent, discoloured, and easily fractured fragile teeth[33]. Certain dentin dysplasias can also lead to early tooth loss[34].

Medical considerations

The differential diagnosis of HPP depends on the age at which the diagnosis is considered and is made by considering this together with any associated bone disorder. For example, in the antenatal period, osteogenesis imperfecta is the main differential diagnosis; just after birth, the differential diagnosis is based on other causes of hypercalcaemia[35]; in childhood, the clinical and radiologic pre-

sentation of HPP can easily be confused with that of other forms of rickets[36]. The differential diagnosis is confirmed by tests indicating lower than normal range levels of serum alkaline phosphatase (ALP), signs of hypomineralisation of the bone, and/or high or normal levels of calcium and serum phosphorus (Table 2)[4,11,36–38,66,67].

Initial evaluation

A patient visiting a dental practice and undergoing clinical evaluation and dental treatment on account of early tooth loss with no prior medical diagnosis may be suffering from a mild or moderate form of HPP (i.e., childhood, adult, or odonto-HPP).

Medical history

Healthcare professionals should always investigate a history of early tooth loss during childhood in the patient and other family members. Early destruction of the periodontium, which in some cases is not associated with an infective or inflammatory context, movement of the teeth, or early tooth loss in adults, may also be warning signs. Additionally, the patient's medical history should be examined for bone problems, rickets, osteomalacia, fractures, osteopenia, osteoporosis, pain, muscle weakness, and craniosynostosis. Other clinical signs may exist, such as muscle weakness and chronic pain, nephrocalcinosis, hypercalciuria, respiratory failure, rheumatic disorders (chondrocalcinosis, osteoarthropathy, pseudogout), and neurological disorders (epileptic seizures, delayed motor development).

Clinical examination

The clinical examination will focus on assessing loss of primary/permanent teeth in relation to the patient's age. An examination of the teeth shed, if they have been kept, may be useful to determine whether the root is almost intact. The mobility of remaining teeth should be assessed together with the health of the periodontium. Radiographs may include a panoramic image and may also include intraoral periapical radiographs of the areas affected, or even assessment by cone beam computed tomography (CBCT). The assessments will vary according to the patient's age and relevant guidelines for the appropriate use of radiographs in dental care[39]. Whereas guidelines for appropriate use of CBCT vary between countries[40–42], it is considered of potential benefit for conditions involving structural or eruption anomalies of teeth, of which HPP is a clear example.

Associated dental abnormalities such as bulbous crowns with cervical constriction, wide pulp chambers, taurodontism of the molars, short roots[43], and hypoplastic enamel should be investigated. Eruption disorders may occur such as eruption retardation[1], ankylosis of the primary teeth, and permanent tooth retention or impaction. These abnormalities are not always present and depend on the severity of the disease.

Table 2. Low alkaline phosphatase (ALP) activity and high concentrations of ALP substrates differentiate hypophosphatasia (HPP) from other disorders and can help ensure an accurate diagnosis[4,11,36–38,66,67].

	Disorder			
	HPP	**Nutritional rickets**	**X-linked hypophosphataemic rickets**	**Osteogenesis imperfecta**
ALP	↓	↑	↑	Normal or transiently ↓
Serum PLP	↑	–	↓	–
Calcium	↑ or normal	↓	Normal	Normal
Phosphate	↑ or normal	↓	↓	Normal
PTH	↓ or normal	↑	Normal	Normal
Vitamin D	Normal	↓	↓ or normal	↓ or normal

ALP, alkaline phosphatase; PLP, pyridoxal-5′-phosphate; PTH, parathyroid hormone.

Laboratory tests

Total serum ALP activity is low in all forms of HPP (Table 2)[14]. If HPP is suspected, it is necessary to request tests to measure serum ALP levels. The ranges shown below are guidelines, and the results should always be considered in relation to the standards issued by the laboratories where the tests are performed, which may vary according to the test methods used.

1) Example guidelines of normal serum ALP levels (male or female adults):
   a) 2–4.5 units (Bondansky)[44]
   b) 4–13 units (King Armstrong)[44]
   c) 40–120 IU/L[14,45]
2) Levels should be compared against specific gender- and age-dependent reference scales for suspicion of HPP[14,45] (Table 3).

Note that a drop in levels of ALP in the blood is not always detectable in the first test; several tests may be necessary in some cases. Additionally, other conditions can lead to low ALP levels, such as pregnancy, certain drugs, hypothyroidism, anaemia, and coeliac disease[4].

For odonto-HPP or nonsevere forms of HPP (childhood or adult HPP), the level of ALP may be closer to the lower limit of normal than in the severe perinatal and infantile forms[46]. Residual enzymatic activity may, in fact, continue, minimising clinical manifestations. In principle, urine phosphoethanolamine tests are carried out only if there is any doubt regarding the diagnosis; levels are elevated in patients with HPP[20]. Serum pyridoxine 5′-phosphate is also elevated and is a sensitive marker for HPP[20]. This assessment in children may then be completed by an analysis of the following parameters: calcium, phosphate, parathyroid hormone, and vitamin D. Radiographs of the left hand and one knee will allow a metaphyseal assessment. These tests will also aid differential diagnosis and rule out other causes of rickets (Table 2)[11].

Table 3. Age- and gender-dependent scales for suspicion of hypophosphatasia[14,45].

	Serum ALP level for suspicion of HPP	
Age range (years)	Males (IU/L)	Females (IU/L)
1–3	≤125	≤125
4–11	≤150	≤150
12–13	≤160	≤110
14–15	≤130	≤55
16–19	≤60	≤40
≥20	≤40	≤40

ALP, alkaline phosphatase; IU/L, international units per litre.

A medical referral is one of the initial steps that should be taken by a dental health professional when a diagnosis of HPP is considered. If HPP is suspected, it may be necessary to pursue an accurate diagnosis by sequencing the defective gene. If there is any doubt, it is absolutely essential to refer the patient and his/her family to a paediatrician, geneticist, and a reference/specialist centre.

Genetic diagnosis

A diagnosis of HPP is made on the basis of the clinical symptoms supported by the results of laboratory tests, that is a low serum ALP level that requires further biological studies and analysis of the *ALPL* gene[4,47]. A genetic consultation is recommended prior to the molecular test. A prenatal genetic diagnosis is possible for families who already have a clinical and molecular diagnosis.

Management

The early loss of primary and/or permanent teeth is almost always a warning sign of a more general illness, and special attention should be paid to the investigation of associated signs. This finding should be reported to the physician in charge of the child or adult patient (paediatrician, general practitioner, geneticist, etc.). This medical diagnosis, supported by the observations of the dental surgeon, is important for the child and his/her family.

Specialist centres

A variety of rare disease resources are available to patients worldwide, including several reference centres for rare diseases (Table 4)[48]. Within Europe, the identification, number,

Table 4. Reference centres dealing with different aspects of hypophosphatasia[48,68].

Region	Country	Centre locations
Europe	Austria	Salzburg
	Belgium	Leuven
	Bulgaria	Sofia
	Cyprus	Nicosia
	Denmark	Aarhus, Copenhagen
	Estonia	Tartu
	France	Amiens, Bordeaux, Brest, Caen, Cayenne, Clermont-Ferrand, Dijon, Le Mans, Lille, Limoges, Lyon, Marseille, Montpellier, Nancy, Nantes, Nice, Nimes, Paris, Pointe à Pitre, Poitiers, Reims, Rennes, Rèunion, Rouen, Saint-Denis, Saint-Etienne, Saint-Laurent-du-Maroni, Strasbourg, Toulon, Toulouse, Tours, Vandoeuvre-Les-Nancy, Vannes
	Germany	Aachen, Berlin, Bonn, Datteln, Düsseldorf, Essen, Freiburg, Hamburg, Hannover, Heidelberg, Köln, Munich, Würzburg
	Hungary	Pecs
	Italy	Acquaviva delle Fonti, Avellino, Belluno, Benevento, Bologna, Cagliari, Campobasso, Catania, Catanzaro, Chieti, Dolo, Florence, Genoa, Imola, Milan, Monza, Naples, Padova, Palermo, Perugia, Pievesestina di Cesena, Pisa, Ragusa, Reggio Emilia, Riga, Rome, Rotondo, Ruffano, San Giovanni Salerno, Siena, Trento, Trieste, Troina, Turin, Udine, Verbania, Verona
	Lebanon	Beirut
	Lithuania	Vilnius
	Morocco	Fes, Rabat
	Netherlands	Amsterdam
	Norway	Oslo
	Portugal	Coimbra, Lisbon, Porto, Vila Real
	Romania	Sibiu
	Russia	Moscow
	Slovenia	Ljubljana
	Spain	Badajoz, Barcelona, Càceres, El Palmar, Madrid, Santander, Seville, Valencia
	Sweden	Stockholm, Uppsala
	Switzerland	Lausanne
	Turkey	Ankara, Istanbul
	United Kingdom	Manchester, Sheffield
Middle East and Africa	Abu Dhabi	Al-Ain
	Saudi Arabia	Riyadh
	South Africa	Randburg
North America	Canada	Montreal, Sherbrooke, Toronto, Winnipeg
	USA	Austin, TX; Chicago, IL; Durham, NC; Indianapolis, IN; Los Angeles, CA; Milwaukee, WI; Nashville, TN; Portland, OR; St. Louis, MO; Durham, NC; Atlanta, GA; Omaha, NE; Houston, TX; Cincinnati, OH; Pittsburgh, PA
Asia Pacific	Australia	Victoria
	Japan	Osaka
	Taiwan	Taipei
South America	Brazil	São Paulo

Reference centre locations may be identified by visiting http://www.orpha.net/consor/cgi-bin/index.php[48].

and distribution of rare disease reference centres vary by member country, along with the services provided[49,50]. Generally, these centres aim to provide countrywide coverage with management structures and named competence centres. They operate in partnership with specialist centres and in collaboration with practitioners in the private sector and highly-skilled local healthcare providers. They are able to guide the dentist or dental surgeon in diagnosis and provide advice on the management and follow-up of these patients. Long-term management is also offered in specialist dental centres, including making paediatric prostheses when the patient is 2.5–3 years of age to compensate for the loss of the primary teeth and managing prosthetic implants in the adult patient[51].

Orthodontic follow-up may be indicated, bearing in mind that treatment should be given with caution on account of the health of the periodontium. Other reference centres/specialist centres that focus on rare calcium and phosphorus disorders and bone

diseases, working as partners (Table 4), can provide support for the patient's medical management.

Treatment

At the time of preparation of this manuscript, the enzyme replacement therapy asfotase alfa (Strensiq™; Alexion Pharmaceuticals Inc, New Haven, CT, USA) is the only available treatment for HPP[52]. It is approved for the treatment of perinatal/infantile- and juvenile-onset HPP in the USA[53], Canada[54], and Europe[55], and for the treatment of HPP in Japan[56]. Asfotase alfa is a recombinant human TNSALP onto which an anchor has been grafted to allow it to affix to the bone[57,58]. This treatment has been tested in a mouse model of HPP with promising results[57,59], in particular in relation to bone mineralisation and the almost total disappearance of orodental signs associated with the disease[60,61]. Spectacular improvements in terms of survival, skeletal manifestation (including healing of rickets), pulmonary function, and growth were reported when asfotase alfa was studied in young children with very severe perinatal or infantile HPP[58]. Other treatments, such as other enzyme replacement therapy or even gene therapy, have also been investigated in animal models[62,63].

Treatment of comorbidities associated with HPP is also important[11]; however, it must be noted that some treatments suitable for bone conditions such as rickets and osteomalacia (high-dose vitamin D, calcium supplements, bisphosphonates) may exacerbate the symptoms of HPP and cause additional problems, such as hypercalcaemia, and should be avoided[11,64].

The importance of setting up a registry

The exact prevalence of HPP is not known, particularly that of the odonto-HPP form. The dentist/dental surgeon can contribute to a better understanding of this dental anomaly and associated rare diseases by registering their patients in the HPP interactive biomedical database, D[4] (Diagnosing Dental Defects Database)/PHENODENT (www.phenodent.org, Strasbourg Cedex, France). On 11 September 2001, the *Comité Consultatif sur le traitement de l'Information en matière de recherche dans le domaine de la Santé* (CCTIRS), a French consultative committee on data processing in health research, issued a favourable opinion of this registry, which was authorised on 18 May 2009 by the *Commission Nationale Informatique et Libertés* (CNIL), the national commission on data processing and protection (registration number 908416).

Global efforts are underway to set up an international registry with the aim of providing a comprehensive, real-life, longitudinal profile of patients with HPP (ClinicalTrials.gov: NCT02306720)[65]. Data concerning patients' treatment and clinical condition will be collected as available from medical records at registry entry (baseline) and a minimum of every 6 months thereafter. The types of information collected will include demographics, HPP disease history and diagnosis, HPP clinical history at baseline, genotypes, biochemical, laboratory and radiologic phenotypes, disease status at follow-up visits, and patient-reported outcomes (such as quality of life, pain/symptoms, and physical function) at baseline and follow-up visits. Patient confidentiality will be maintained throughout. As of 1 June 2015, eight patients have been enrolled. Three sites are active in two countries (the USA and the UK), and sites in eight additional countries are in the process of being activated in anticipation of starting the broader phase of the study (France, Germany, Spain, Russia, Czech Republic, Austria, Belgium, and Italy).

This special effort is being made to register patients affected by any form of HPP because of the development of pharmaceutical treatments including enzyme replacement therapy. Analysis of information gathered by the HPP registry study will lead to a better understanding of HPP which, in turn, will increase awareness, aid diagnosis, and improve patient care.

Identification of a cohort

Registration of patients with HPP in the registry will make it possible to create an HPP

cohort. This is a real benefit for patients with HPP who may not currently benefit from a specialist opinion covering all aspects of their condition as part of their treatment plan. Creating a cohort will inevitably enhance patient management and lead to a follow-up system that is not fragmented, but which is also in harmony with the different aspects of management that will be needed throughout the patient's life.

Recording of the natural history of the disease

It is important to characterise the process of the disease, to understand its variable presentation, and identify markers of disease progression. Such information is essential to the selection of patients who might benefit from treatment and for the evaluation of the efficacy of any treatment. Although various therapeutic approaches are being developed, it is possible that not all patients will be suitable for the same medication or the same treatment regimen. A better understanding of patients and a clearer picture of their condition will make it easier to select the medication to be administered.

Development of a specific database

It is necessary to collect precise information on different aspects of HPP and to have a single tool for recording information such as genotype (type of genetic defect), phenotype (whether bone or teeth related), the course of the disease, any treatment that may have been given, and quality of life. Currently, these data are fragmented for each individual patient; they may be collected in some cases, but generally focus on one specific problem or area. The idea of such a database is to allow information to be shared between specialists in all areas of HPP (e.g., growth, metabolism of bone, phosphorus and calcium, genetics, oral cavity, pain). A quality-of-life module and the ability to include data provided by patients are very important for assessment of the impact of the disease and its course.

Often, healthcare professionals may only be able to focus on their area of expertise, possibly due to various constraints in healthcare systems, and may not have access to information and resources on other aspects of the disease. As a result, they might not be able to provide a holistic approach to the management of HPP, and different specialties may need to be involved in the care of different manifestations of the disease. For the healthcare professional, therefore, the ability to access all the patient's data in a central registry will be extremely important. Orodental issues are closely linked to disease severity; therefore, this information is important to share.

Limited data are available on the course of the disease in HPP, hence the importance of patient follow-up. With regard to teeth, little information is available to allow a comparison of primary teeth history (e.g., the number of teeth lost) with status of the permanent teeth. In fact, reports are generally produced and issued at a given time, and there is no multiaspect, multiprofessional follow-up of patients over time. Follow-up of this type may improve our knowledge of the natural history of HPP and also make it possible to identify patients who would be candidates for treatment.

This research tool may provide a better understanding of the disease, a better understanding of the link between clinical signs (phenotype) and the genotype of this disease, the identification of more patients, the discovery of new genes behind such cases of HPP, the identification of modifying genes, and the evaluation of treatments.

What action should be taken if the diagnosis is suspected or confirmed?

It is of great importance for patients and their treating practitioners to liaise with reference and other specialised centres to benefit from coordinated management of HPP, from clinical and molecular diagnosis to treatment and registry participation.

HPP patient support groups worldwide help patients and their families understand and deal with every aspect of the disease (Table 5). They are a source of accurate, up-to-date information for patients, especially with regard to treatment development and research. These support groups may promote

Table 5. Hypophosphatasia Patient Support Groups.

Name	Contact Information	Activities
Hypophosphatasie Europe	16 rue Barbanègre 68330 – Huningue, France contact@hypophosphatasia.eu www.hypophosphatasia.eu	Established in 2004, the group brings together patients and families, healthcare professionals and the general public with an interest in HPP in many projects and initiatives
Soft Bones Foundation	121 Hawkins Place, #267. Boonton, New Jersey 07005, USA +1 973 453 3093 +1 866 827 9937 http://softbones.org/	Provides information, education and support for people with HPP, their families and caregivers; promotes research of the disease through awareness and fundraising efforts
Hypophosphatasie Deutschland e.V	Rottendorfer Straße 1, 97072 Würzburg, Germany +49 0931 782937 http://www.hpp-ev.de	Provides comprehensive awareness of symptoms and problems of patients with HPP to the general public and medical professionals. Assists affected families by providing a forum for the exchange of experiences and discovery of the latest research, as well as direct assistance in times of crisis. The association implements new research projects into HPP and its treatment
HPP-Choose Hope	8429 Indigo Sky Ave, Las Vegas, NV 89129 +1 855 477 7273 info@hppchoosehope.org http://hppchoosehope.org/	Raises funds through the HPP-Choose Hope Foundation for research into treatments and a cure for HPP, and provides education to physicians and families about HPP
HypoPhosPhatasia Support Association of Japan (HPPSA-J)	http://hypophosphatasia.life.coocan.jp/	Supports interaction and information exchange between HPP patients and families via a message board and mailings exclusively for association members. Information on causes of HPP, symptoms, treatment methods and the latest research developments is also posted. HPPSA-J conducts activities to raise awareness of HPP, and is working towards designating HPP as a specified chronic childhood disease and specified disease (classification of the Japanese government)

research programs, seek funding and engage in various activities, and create educational materials to help increase knowledge and awareness of HPP.

Further information

Further information can be obtained from Orphanet, the European portal for rare diseases and orphan drugs, sections on HPP www.orpha.net, www.hypophosphatasia.com, and OMIM (http://www.ncbi.nlm.nih.gov/omim) numbers 146300, 241510, and 241500.

Prof. Etienne Mornet maintains a database of known *ALPL* gene mutations at http://www.sesep.uvsq.fr/03_hypo_mutations.php. As of 6 October 2015, a total of 300 mutations have been described.

Conclusions

In a patient presenting with unexplained premature primary and/or permanent tooth loss, the dental surgeon, and especially the paediatric dentist, is at the heart of the challenges associated with the diagnosis, management, and follow-up of patients with HPP. Dental surgeons must play an active part in national and international initiatives to identify patients with HPP through their participation and inclusion in a rare diseases register. This voluntary action will support enhanced knowledge and evidence-based orodental medicine.

Why this paper is important to paediatric dentists

- Dentists and dental surgeons can play an active part in initiatives to identify patients with HPP through their participation in a rare disease registry
- This voluntary action will support efforts to enhance knowledge of and obtain evidence-based data relating to HPP in orodental medicine
- Early identification of patients can improve access to life-changing therapy

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Conflicts of Interest

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References

1 Bianchi ML. Hypophosphatasia: an overview of the disease and its treatment. *Osteoporos Int* 2015; **26**: 2743–2757.
2 Mornet E, Hofmann C, Bloch-Zupan A, Girschick H, Le Merrer M. Clinical utility gene card for: hypophosphatasia— update 2013. *Eur J Hum Genet* 2014; **22**: doi: 10.1038/ejhg.2013.177.
3 Millan JL. The role of phosphatases in the initiation of skeletal mineralization. *Calcif Tissue Int* 2012; **93**: 299–306.
4 Mornet E. Hypophosphatasia. *Orphanet J Rare Dis* 2007; **2**: 40.
5 Lezot F, Descroix V, Hotton D, Mauro N, Kato S, Berdal A. Vitamin D and tissue non-specific alkaline phosphatase in dental cells. *Eur J Oral Sci* 2006; **114** (Suppl. 1): 178–182.
6 Whyte MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. *Ann N Y Acad Sci* 2010; **1192**: 190–200.
7 Millart H, Lamiable D. Determination of pyridoxal 5′-phosphate in human serum by reversed phase high performance liquid chromatography combined with spectrofluorimetric detection of 4-pyridoxic acid 5′-phosphate as a derivative. *Analyst* 1989; **114**: 1225–1228.
8 Shin YS, Rasshofer R, Friedrich B, Endres W. Pyridoxal-5′-phosphate determination by a sensitive micromethod in human blood, urine and tissues; its relation to cystathioninuria in neuroblastoma and biliary atresia. *Clin Chim Acta* 1983; **127**: 77–85.
9 Ryan LM, Kozin F, Mccarty DJ. Quantification of human plasma inorganic pyrophosphate. *Arthritis Rheum* 1979; **22**: 892–895.
10 Silcox DC, McCarty DJ. Measurement of inorganic pyrophosphate in biological fluids, elevated levels in some patients with osteoarthritis, pseudogout, acromegaly, and uremia. *J Clin Invest* 1973; **52**: 1863–1870.
11 Rockman-Greenberg C. Hypophosphatasia. *Pediatr Endocrinol Rev* 2013; **10** (Suppl. 2): 380–388.
12 Wenkert D, McAlister WH, Coburn SP *et al.* Hypophosphatasia: nonlethal disease despite skeletal presentation in utero (17 new cases and literature review). *J Bone Mineral Res* 2011; **26**: 2389–2398.
13 Whyte MP, Zhang F, Wenkert D *et al.* Hypophosphatasia: validation and expansion of the clinical nosology for children from 25 years' experience with 173 pediatric patients. *Bone* 2015; **75**: 229–239.
14 Mornet E, Nunes ME. Hypophosphatasia. In: Pagon RA, Bird TD, Dolan CR, Stephen K (eds). Gene Reviews. Seattle, WA: University of Washington, Seattle, 2010.
15 Whyte MP. Hypophosphatasia. In: Thakker RV, Whyte MP, Eisman JA, Igarashi T (eds). Genetics of Bone Biology and Skeletal Disease. New York: Academic Press, 2013: 337–360.
16 Hui M, Tennenbaum HC. New face of an old enzyme: alkaline phosphatase may contribute to human tissue aging by inducing tissue hardening and calcification. *Anat Rec* 1998; **253**: 91–94.
17 Mornet E, Yvard A, Taillandier A, Fauvert D, Simon-Bouy B. A molecular-based estimation of the prevalence of hypophosphatasia in the European population. *Ann Hum Genet* 2011; **75**: 439–445.
18 Taketani T, Onigata K, Kobayashi H, Mushimoto Y, Fukuda S, Yamaguchi S. Clinical and genetic aspects of hypophosphatasia in Japanese Patients. *Arc Dis Child* 2014; **99**: 211–215.
19 Fraser D. Hypophosphatasia. *Am J Med* 1957; **22**: 730–746.

20 Leung EC, Mhanni AA, Reed M, Whyte MP, Landy H, Greenberg CR. Outcome of perinatal hypophosphatasia in Manitoba Mennonites: a retrospective cohort analysis. *JIMD Rep* 2013; **11**: 73–78.
21 Reibel A, Maniere MC, Clauss F *et al.* Orodental phenotype and genotype findings in all subtypes of hypophosphatasia. *Orphanet J Rare Dis* 2009; **4**: 6.
22 Bloch-Zupan A, Sedano H, Scully C. Dento/Oro/Craniofacial Anomalies and Genetics. London: Elsevier Inc., 2012.
23 Bloch-Zupan A. Hypophosphatasie: diagnostic et signes cliniques. *Alpha Omega News* 2014; **166**: 23–26.
24 Bloch-Zupan A, Mornet E. L'Odontohypophosphatasie. *Le Chirurgien Dentiste de France* 2005; **1235**: 27–29.
25 Foster BL, Nagatomo KJ, Nociti FH Jr *et al.* Central role of pyrophosphate in acellular cementum formation. *PLoS ONE* 2012; **7**: e38393.
26 van den Bos T, Handoko G, Niehof A *et al.* Cementum and dentin in hypophosphatasia. *J Dent Res* 2005; **84**: 1021–1025.
27 Schlosser BJ, Pirigyi M, Mirowski GW. Oral manifestations of hematologic and nutritional diseases. *Otolaryngol Clin North Am* 2011; **44**: 183–203.
28 Sreeramulu B, Shyam ND, Ajay P, Suman P. Papillon-Lefèvre syndrome: clinical presentation and management options. *Clin Cosmet Investig Dent* 2015; **7**: 75–81.
29 Pahwa P, Lamba AK, Faraz F, Tandon S. Haim-Munk syndrome. *J Indian Soc Periodontol* 2010; **14**: 201–203.
30 Rezende KM, Canela AH, Ortega AO, Tintel C, Bönecker M. Chediak-Higashi syndrome and premature exfoliation of primary teeth. *Braz Dent J* 2013; **24**: 667–670.
31 Abel MD, Carrasco LR. Ehlers-Danlos syndrome: classifications, oral manifestations, and dental considerations. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006; **102**: 582–590.
32 Naulin-Ifi C. Odontologie Pédiatrique Clinique. JPIO. (CdP Cahiers de prothèses éditions) Initiatives Santé, Malakoff, 2011.
33 National Institutes of Health. Osteoporosis and Related Bone Diseases ~ National Resource Center. Guide to Osteogenesis Imperfecta for Pediatricians and Family Practice Physicians. 2007; www.niams.nih.gov/bone [cited January 27, 2016].
34 Malik S, Gupta S, Wadhwan V, Suhasini GP. Dentin dysplasia type I - A rare entity. *J Oral Maxillofac Pathol* 2015; **19**: 110.
35 Bishop N. Clinical management of hypophosphatasia. *Clin Cases Miner Bone Metab* 2015; **12**: 170–173.
36 Nield LS, Mahajan P, Joshi A, Kamat D. Rickets: not a disease of the past. *Am Fam Physician* 2006; **74**: 619–630.
37 Mohn A, De Leonibus C, de Giorgis T, Mornet E, Chiarelli F. Hypophosphatasia in a child with widened anterior fontanelle: lessons learned from late diagnosis and incorrect treatment. *Acta Paediatr* 2011; **100**: e43–e46.
38 Reynolds RD, Lorenc RS, Wieczorek E, Pronicka E. Extremely low serum pyridoxal 5′-phosphate in children with familial hypophosphatemic rickets. *Am J Clin Nutr* 1991; **53**: 698–701.
39 American Dental Association, US Food & Drug Administration. The Selection of Patients for Dental Radiograph Examinations. http://www.ada.org/sections/advocacy/pdfs/topics_radiography_examinations(1).pdf.
40 Mallya SM. Evidence and professional guidelines for appropriate use of cone beam computed tomography. *J Calif Dent Assoc* 2015; **43**: 512–520.
41 American Dental Association Council on Scientific Affairs. The use of cone-beam computed tomography in dentistry: an advisory statement from the American Dental Association Council on Scientific Affairs. *J Am Dent Assoc* 2012; **143**: 899–902.
42 American Academy of Oral and Maxillofacial Radiology. Clinical recommendations regarding use of cone beam computed tomography in orthodontics. [corrected]. Position statement by the American Academy of Oral and Maxillofacial Radiology. *Oral Surg Oral Med Oral Pathol. Oral Radiol* 2013; **116**: 238–257.
43 Foster BL, Ramnitz MS, Gafni R *et al.* Rare Bone Diseases and Their Dental, Oral, and Craniofacial Manifestations. *J Dent Res* 2014; **93** (Suppl.): 7S–19S.
44 National Cancer Institute. http://training.seer.cancer.gov/abstracting/procedures/clinical/hematologic/serum.html [updated March 15, 2015].
45 ARUP Laboratories. Alkaline phosphatase isoenzymes, serum or plasma. ARUP Laboratories website; http://ltd.aruplab.com/tests/pub/0021020 [updated March 15, 2015].
46 Whyte MP. Hypophosphatasia. In: Glorieux FH, Jueppner H, Pettifor J (eds). Pediatric bone: biology & diseases, 3rd edn. San Diego, CA: Elsevier (Academic Press); 2012: 771–794.
47 Taillandier A, Domingues C, De Cazanove C *et al.* Molecular diagnosis of hypophosphatasia and differential diagnosis by targeted Next Generation Sequencing. *Mol Genet Metab* 2015; **116**: 215–220.
48 Orphanet Portal for Rare Diseases and Orphan Drugs; http://www.orpha.net/consor/ [updated June 28, 2015].
49 European Commission on Public Health; http://ec.europa.eu/health/rare_diseases/european_reference_networks/erf/index_en.htm#fragment1 [updated June 23, 2015].
50 Bloch-Zupan A, Manière MC. Manifestations Odontologiques des Maladies Rares. Centre de Référence de Strasbourg. *Alpha-Omega News* 2008; **118**: 4–6.
51 Lynch CD, Ziada HM, Buckley LA, O'Sullivan VR, Aherne T, Aherne S. Prosthodontic rehabilitation of hypophosphatasia using dental implants: a review of the literature and two case reports. *J Oral Rehabil* 2009; **36**: 462–468.
52 FDA Approves Strensiq™ (asfotase alfa) for Treatment of Patients with Perinatal-, Infantile- and

Juvenile-Onset Hypophosphatasia (HPP); http://news.alexionpharma.com/press-release/product-news/fda-approves-strensiq-asfotase-alfa-treatment-patients-perinatal-infantil [updated 22 January 2016].
53 Strensiq™ U.S. Prescribing Information, 2015. Alexion Pharmaceuticals, Inc. Cheshire, CT. http://www.strensiq.com/images/pi.pdf. [updated 21 January 2016].
54 Health Canada Approves Strensiq™ (asfotase alfa), the First Therapy for Patients with Hypophosphatasia (HPP), an Ultra-rare, Life-threatening Disease. http://www.newswire.ca/news-releases/health-canada-approves-strensiq-asfotase-alfa-the-first-therapy-for-patients-with-hypophosphatasia-hpp-an-ultra-rare-life-threatening-disease-522085271.html [updated 27 January 2016].
55 European Commission Grants Marketing Authorization for Strensiq™ (asfotase alfa) for the Treatment of Patients with Pediatric-Onset Hypophosphatasia (HPP). http://news.alexionpharma.com/press-release/company-news/european-commission-grants-marketing-authorization-strensiq-asfotase-alfa [updated 27 January 2016].
56 Strensiq® (asfotase alfa) Receives Marketing Approval in Japan for Treatment of Patients with Hypophosphatasia (HPP). http://news.alexionpharma.com/press-release/company-news/strensiq-asfotase-alfa-receives-marketing-approval-japan-treatment-patien [updated 27 January 2016].
57 Millan JL, Narisawa S, Lemire I *et al.* Enzyme replacement therapy for murine hypophosphatasia. *J Bone Miner Res* 2008; **23**: 777–787.
58 Whyte MP, Greenberg CR, Salman NJ *et al.* Enzyme-replacement therapy in life-threatening hypophosphatasia. *N Engl J Med* 2012; **366**: 904–913.
59 Yadav MC, Lemire I, Leonard P *et al.* Dose response of bone-targeted enzyme replacement for murine hypophosphatasia. *Bone* 2011; **49**: 250–256.
60 Foster BL, Nagatomo KJ, Tso HW *et al.* Tooth root dentin mineralization defects in a mouse model of hypophosphatasia. *J Bone Miner Res* 2013; **28**: 271–282.
61 Yadav MC, de Oliveira RC, Foster BL *et al.* Enzyme replacement prevents enamel defects in hypophosphatasia mice. *J Bone Miner Res* 2012; **27**: 1722–1734.
62 Sugano H, Matsumoto T, Miyake K *et al.* Successful gene therapy in utero for lethal murine hypophosphatasia. *Hum Gene Ther* 2012; **23**: 399–406.
63 Gasque KCS, Foster BL, Kuss P *et al.* Improvement of the skeletal and dental hypophosphatasia phenotype in $Alpl^{-/-}$ mice by administration of soluble (non-targeted) chimeric alkaline phosphatase. *Bone* 2015; **72**: 137–147.
64 Cundy T, Michigami T, Tachikawa K *et al.* Reversible deterioration in hypophosphatasia caused by renal failure with bisphosphonate treatment. *J Bone Miner Res* 2015; **30**: 1726–1737.
65 Kishnani PS, Langman CB, Linglart A *et al.* A longitudinal, prospective, long-term registry of patients with hypophosphatasia. *Bone Abstracts* 2015; **4**: P154.
66 McKiernan FE, Berg RL, Fuehrer J. Clinical and radiographic findings in adults with persistent hypophosphatasemia. *J Bone Miner Res* 2014; **29**: 1651–1660.
67 Chevrel G. Osteogenesis imperfecta. Orphanet encyclopedia, June 2004. https://www.orpha.net/data/patho/GB/uk-OI.pdf [updated 27 January, 2016].
68 Martins L, Rodrigues TL, Ribeiro MM *et al.* Novel ALPL genetic alteration associated with an odonto-hypophosphatasia phenotype. *Bone* 2013; **56**: 390–397.